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Editorial

Assessing equivalence of inhaled drugs

The move to disease management has led to an increase in the practice of drug or formulation substitution on the basis of equivalence. Well established guidelines are available for judging equivalence between oral, but not inhaled, formulations. This article describes the criteria by which equivalence can be assessed and concludes that although traditional issues such as adequate sample size are important, studies also need to be designed in such a way as to avoid the possibility of falsely concluding clinical equivalence.

Introduction

The new trend towards disease management raises important issues as there are increasing demands to reduce the number of drugs/formulations stored within a pharmacy, and in some countries substitutions between formulations is taking place. For the treatment of obstructive airway disease, although the number of different classes of inhaled drugs remains small, there is an increasing number of drugs within each class. In addition, any one drug may have different types of formulation, i.e. powder or metered dose inhaler (MDI), and may even have a number of formulations within each of those types on the market. In a recurrent Workshop (1), general points on equivalence testing of inhalers was discussed. This article will discuss the criteria by which different drugs for formulations should be compared to determine their equivalence, which would enable rational pharmacy stocking and substitution.

Usually a new drug in a therapeutic class has its safety and efficacy profile fully established within the registration process. However, approval for a change in formulation may be based on much less data, even data limited to pharmaceutical rather than clinical performance. It is therefore in the latter case where careful assessment of the data is required.

Clear differences between drugs or formulations can be established relatively easily by statistical studies to reject the Null hypothesis. However, the presence of true equivalence is not so readily proven, as poor study design or interpretation can result in the perception of equivalence which is in fact not the case. Apparent equivalence can lead to the use of drugs with reduced efficacy or increased risk, both of which would be unacceptable when safe and effective drugs and formulations are already available. The problems of such apparent equivalence were highlighted at a Food and Drug Administration (FDA) advisory meeting on generic drugs in the U.S.A. At that meeting, Cuss showed data comparing a salbutamol MDI and powder formulation which had identical efficacy, but the powder formulation gave increased systemic side-effects. Such a difference between formulations has been shown in another study comparing salbutamol powder to terbutaline powder, where a similar efficacy but a different safety profile was observed (2). These cases did not show apparent equivalence but they do raise the need for close scrutiny of the available data.

History of Equivalence Testing

Two decades ago it was common practice to demonstrate bioequivalence of drug formulations by comparing blood levels in only a few volunteers (often six or less), with the consequence that only massive differences in formulations could be detected statistically. The low statistical power inevitably resulted in a complete lack of any statistical difference which was often misinterpreted as strong evidence that the two formulations were equivalent. Thus lack of evidence for showing a difference was taken as evidence of no difference between the drugs, rather than concluding that the very limited data did not support any conclusion. This led to gradual demands for bigger studies which caused the opposite effect, i.e. rejection of reasonable pharmaceutical bioequivalence because of statistical detection of trivially small differences. The more one tried to demonstrate bioequivalence by using large sample sizes, the more likely it became that bioequivalence would be rejected. This paradox was finally resolved by Schuirmann who in 1987 (3) proposed a new confidence interval approach which was subsequently adopted as the FDA Guidelines in 1992 (4). The principle behind this is to first define the maximum difference that is acceptable between formulations for them to still be accepted as clinically equivalent. The

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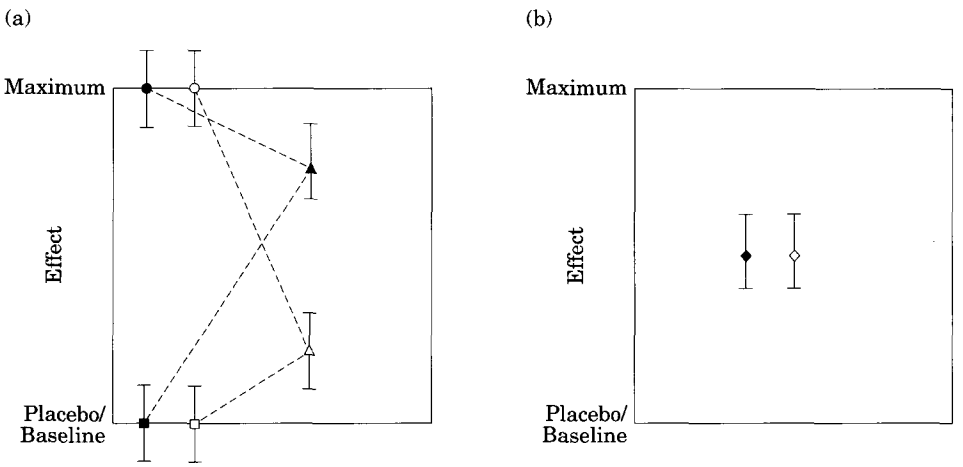

Fig. 1 The potential pitfalls of equivalence studies. (a) Potential false equality. Two formulations were studied in patients with mild, moderate and severe asthma. In mild and severe asthma they are apparently equivalent. However, in moderate asthma there is a clear difference between formulations. (b) True equality. This shows how the data should look in a true equivalence study. The results of the two formulations show equivalence, both formulations are clearly more effective than placebo and less effective than maximum. ■, □, severe asthma; ▲, △, moderate asthma; ●, ○, mild asthma.

statistical test hypothesis is then re-arranged so that the confidence intervals of the differences have to fall within set limits (usually ± 20%). This principle has the effect that increased sample size results in a greater chance of statistically rejecting 'non-equivalence' of two equivalent formulations. This statistical approach is appropriate for determining bioequivalence as measured by pharmacokinetic parameters of drug blood levels. However, when applied to clinical efficacy parameters, there are additional factors which can give rise to a misleading or an apparent conclusion.

Single Dose Clinical Studies

The pharmacokinetic approach can be applied to single dose studies measuring lung function parameters, e.g. assessing peak effect of bronchodilators. There can be little doubt that a study which demonstrates identical dose–response over the same dose range of the same or similar drugs with adequate sample size gives acceptable information to claim equivalence (5). The same would be true for relative safety if systemic effects were measured, for example, with a β-agonist (6). However, even cumulative dose–response data can be misleading if the dose range is different or the duration of action of the drugs is not equal, as with such a design the influence of the earlier dosing will alter the response to subsequent doses.

It is also possible to design single dose studies to compare the duration of action of inhaled drug if the following criteria are included. First, the data must achieve the criteria for equivalence *vis-à-vis* the pharmacokinetic study. In addition, the response must be statistically less than the maximum achieved in the patients' group by a reference drug (short acting β_2-agonist) and greater than placebo or baseline. (Fig. 1). Similar design can be applied to bronchial challenge which can be a useful parameter for measuring both bronchodilators and drugs such as sodium cromoglycate. There is, however, no single dose study appropriate for comparing glucocorticosteroids, as single dose pharmacokinetic studies with corticosteroids only give information about safety and no efficacy interpretation can be made. Therefore, a multiple dose approach is required.

Multiple Dose Clinical Studies

Multiple dose studies have similar pitfalls to single dose studies. The primary efficacy variable must fulfil the criteria for equivalence. However, as with single dose studies, there are two outcomes where data providing adequate statistical equivalence may in fact be demonstrating misleading clinical equivalence. These are when both treatments have no effect (7) or when both treatments have had the maximum possible effect in the patients (8). To ensure that this will not happen, all multiple dose studies should incorporate a determination of the maximum possible shift in a primary efficacy variable. This could be achieved by giving a standard dose of a bronchodilator. If possible, all studies should contain

a placebo limb. Then, the data must show that both treatments have significantly more effect than placebo and that the effect is below the maximum value before true equivalence can be inferred (Fig. 1). If placebo limbs are not ethically possible, it may be acceptable to compare study data with a prolonged stable run-in to make the judgement that both drugs have had an effect.

Conclusion

The demonstration of equivalence between inhaled drugs requires special consideration as the pharmacokinetic approach used for oral drugs is relevant for side-effects, not efficacy of topical formulations. However, the same statistical principle that determines the equivalence can be used if the study design is adequate in addressing the following points.

First, will the sample size be adequate to have ensured that the study had enough statistical power to detect non-equality if it was present? Second, will any evidence be obtained to show that the treatments were better than placebo or at least baseline? Third, will the responses be below the maximum possible clinical change?

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